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The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers

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Abstract

There are a multitude of formulation factors to consider when developing a pMDI. Evaluation of each of these variables has been performed over the years, but there has been an abundance of different approaches in the determination of the effects on device performance. Thus, although much is known about pMDI on the empirical level, a systematic approach has clearly been missing. With the ratification of the Montreal Protocol and the introduction of alternative propellant systems, the opportunity to establish relationships between different levels of testing, such as in vitro measurements and in vivo outcomes, and in vivo assessments and clinical outcomes, has arrived. This review outlines research efforts that have focused on the formulation of propellant-driven metered dose inhalers using alternative propellants. These formulation factors, including device characteristics, are reviewed with respect to the performance of MDIs.

Keywords: Asthma; Hydrofluoroalkane; Aerosol; Chlorofluorocarbon; Vapor pressure; Particle size; Lung deposition

Contents

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1. Introduction

Aerosolized beta agonists and anti-allergic compounds were first formulated as pharmaceutical aerosols in 1956 using chlorofluorocarbons (CFCs). CFC propellants possessed several desirable characteristics that prompted their use in propellant-driven metered dose inhalers (pMDIs) that include non-toxicity, inertness, and high vapor pressures. Generally, metered dose inhaler formulations containing CFCs combine a blend of propellants, excipients, and drug substance such that formulation factors and device characteristics combine to generate an efficient spray for delivery to the lungs. However, the manufacture of CFC propellants was eliminated after the signing of the Montreal Protocol [1]. The phase-out of CFCs was in response to concern over possible detrimental effects on the ozone layer originally raised in the 1970s [2]. Since this original hypothesis, stratospheric ozone depletion has been demonstrated over the Antarctic [3]. In the United States, the Food and Drug Administration has recently set standards for the use of ozone-depleting substances and so-called 'essential-use' determinations [4]. Specifically, for propellant-driven metered dose inhalers determined not to have continued essentiality, the following points were made: (1) products that are no longer marketed, and (2) products containing ozone-depleting substances marketed after January 1, 2005, may be proposed to be non-essential, (3) a moiety can remain on the essential-use list until a non-ozone-depleting product is marketed (same route of administration, indication, and convenience), has sufficient supplies to meet patient needs, and has sufficient post-marketing data, and (4) a CFC-MDI will not be removed until at least two non-ozone-depleting alternative products are marketed under more than one new drug application.

Accordingly, alternative systems for the delivery of inhaled medications have been an active research focus in recent years. Several different approaches have been adopted and include alternative propellant systems, propellant-free liquid methods, and dry powder inhaler-based devices [5–7]. This article will outline research efforts that have focused on the reformulation of CFC-based metered dose inhalers using alternative propellants. Predominantly this relates to the use of hydrofluorocarbon (HFC) propellants and the accompanying formulation strategies that have developed alongside this substitution effort. These formulation factors, including device characteristics, are reviewed with respect to the performance of MDIs.

2. Metered dose inhaler design

Several types of devices are used to deliver a metered dose of aerosolized medication to the respiratory tract. However, pMDIs are specifically recognized as those devices that incorporate a propellant, under pressure, to generate a metered dose of an aerosol through an atomization nozzle. MDIs are the most widely used respiratory drug delivery device, with an estimated 800 million units produced in 2000

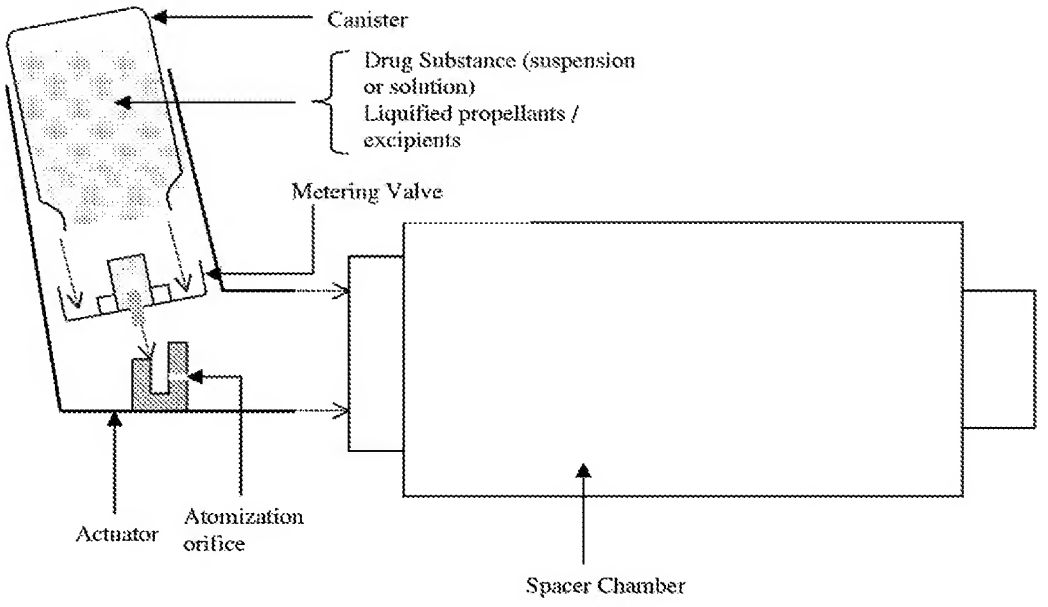

Fig. 1. Basic components of a pMDI system.

[8]. MDIs consist of several components (Fig. 1): the active substance formulated with propellant and excipients, a container, a metering valve crimped onto the container, an actuator that connects the metering valve to an atomization nozzle, and a mouth piece. Additionally, holding chambers or spacers may also form part of the delivery system by connection to the actuator mouthpiece. A metered volume (typically between 20 and 100 μl) of the drug/excipient/propellant blend is expelled from the canister via the valve and quickly passes through the actuator orifice where primary atomization occurs. Characterization of aerosol clouds emitted from pMDIs is difficult due to the dynamics of the atomization process [9]. Individual droplets and the surrounding environment of the droplets change rapidly in terms of size, velocity, and position after being emitted from the actuator orifice. The interaction of this dynamic aerosol plume with the geometry of the mouth and airways determines the extent of oral and lung deposition. Mechanisms of deposition include inertial impaction, sedimentation, diffusion, interception, and electrostatic precipitation [10]. The relative importance of each deposition mechanism on an individual droplet therefore depends on a multitude of factors such as droplet size, velocity, evaporation rates, and the anatomical features of the patient's airways.

3. Measures of the performance of MDIs

3.1. Performance of current pMDI devices

The transition of pMDIs from CFC to HFC systems has provided an opportunity for the pharmaceutical industry to re-evaluate inhaler performance. From one point of view, the task might be seen as showing equivalence between the CFC systems and their replacements. This approach to the transition is less problematic in terms of regulatory approval and is therefore more cost effective in the short term. However, recent phenomenological reports comparing CFC systems to HFA systems suggest that a 'detuning' of the HFA formulations is necessary to attain regulatory equivalence between the systems [11]. Thus, the opportunity has arisen to improve inhaler performance using a systematic approach of evaluating the effect of formulation and device factors on pMDI performance.

Inhaled therapy for treatment of asthma is targeted such that the active drug substance is delivered topically. In terms of bronchodilators this has the primary advantage of rapid onset of action, but also minimizes the risk of unwanted systemic side-effects, which is particularly important in corticosteriod therapy. However, simply targeting the lung as an organ may not result in optimal therapy, as the target receptors for a specific drug may be located in particular regions of the lung [12]. Furthermore, none of the available anti-asthma drugs are metabolized in the lungs [13]. Consequently, the drug delivered to the lung will eventually reach the systemic circulation and contribute to systemic activity. Thus, the effectiveness of inhaled therapy for topical diseases such as asthma depends on the device to deliver the correct dose of active drug substance to the site of action with minimal deposition to other regions that may contribute to unwanted side-effects. As a result, measurement and assessment of inhaled drug delivery is very complex due to the multitude of variables that contribute to variations in delivery such as drug formulation, delivery device, administration skill, breathing pattern, and lung pathology/anatomy [14]. Also, the optimal outcome may not be defined identically between scientists, clinicians, patients, regulatory agencies, and those paying for the cost of treatment [14].

3.2. In vivo determination of pMDI performance

Measures of respiratory drug delivery performance include pharmacokinetic/pharmacodynamic investigations, in vivo measures, in vitro tests, and also mathematical models of deposition. All measures are important in optimizing the development of drug formulations and delivery devices for the appropriate clinical outcome. Pharmacokinetic/pharmacodynamic studies involve measuring plasma drug/physiological marker concentrations and correlating them with clinical efficacy and toxicity. This approach allows elucidation of the relationship between drug delivery and efficacy/toxicity, but may be complicated by assay limits, local metabolism and gastrointestinal absorption. Used in conjunction with in vitro and scintigraphic studies, specific characteristics of formulation and device development can be related to the clinical outcome. Scintigraphic studies allow visualization of regional lung deposition by incorporation of a gamma-radiating nuclide into the formulation [15]. The site and quantitative amount of deposition can be calculated, making this technique integral to device and formulation development as well as being useful in drug targeting studies [15]. Used alone, however, this technique does not measure clinical efficacy or toxicity. A number of clinical outcomes are also essential for evaluation of inhaled therapy. Spirometry, peak expiratory flow (PEF), bronchoprovocation testing, measurement of inflammation markers, toxicity, quality of life measures, and epidemiological studies have all been widely used to evaluate the performance of formulations and devices in asthma therapy [14]. The performance of formulations and devices for bronchodilator delivery to the lung can be assessed using changes in lung function (such as spirometry and PEF). However, there are no such immediate measures to determine the performance of devices containing anti-inflammatory agents for the prevention of asthma. In these cases, the clinical response to regional lung delivery may be assessed using tissue biopsy and bronchoalveolar lavage samples or indirect measures that include urinary and serum cortisol levels [16,17].

3.3. Models and mechanisms of deposition within the airways

The importance of in vitro measurements in pMDI development and optimization can be appreciated with an understanding of the mechanisms of particle deposition in the lungs. As already mentioned, inertial impaction, sedimentation, diffusion, interception, and electrostatic precipitation are the significant mechanisms that dictate where a droplet or particle will deposit in the airways. Inertial impaction in the lung occurs when particles of sufficient momentum (a product of mass and velocity) are unable to follow the curved streamlines of air within the airways during inhalation due to significant centrifugal forces [18]. Sedimentation of particles within the airways is related to particle mass and residence times [19]. Deposition via diffusion is often a small but sometimes significant mechanism, particularly when particle size is sufficiently small [10]. Significant deposition via interception occurs when the dimensions of

the anatomic spaces of the airways become comparable to those of the particle [10]. Finally, electrostatic precipitation may sometimes occur when charged particles, typically charged during atomization, are electrostatically attracted by a charge of opposite sign. Such charges may already be present on the walls of the device or airways or may be induced by the charged particle itself [10]. Data indicate that small particles (<1 μm) are most influenced, but the overall significance is unknown for pMDIs [18]. The extent and location of deposition of pMDI aerosols can be modeled empirically or by using mechanistically based approaches [19]. Despite being over-simplifications of aerosol deposition, these models are very useful in demonstrating the effect of certain variables influencing deposition in the lung. Although there are a multitude of models available in the literature [19,20], each predicts that particle diameter and airway diameter have the potential to influence particle deposition the most [19]. Thus, given that particle diameter in under more control in terms of formulation and device selection, it is generally accepted that particle size is the single most important parameter in pharmaceutical aerosol delivery.

3.4. In vitro measures of pMDI performance

Given the complexity of the interactions of aerosol clouds emitted by pMDIs and the airways, it is difficult to define simple measures of device and formulation performance. However, in vitro methods have been developed that measure particle size and emitted dose characteristics of aerosol drug delivery devices. Both theoretical calculations derived from models such as those mentioned above and experimental deposition studies using stable monodisperse aerosols suggest particle size data can be used as an estimate of aerosol deposition efficiency [10]. These predictions indicate that particles greater than around 6 μm will be deposited in oropharyngeal regions and will not enter the lung [10], while particles that traverse the pharynx and upper airways are generally less than 6 μm [21]. In addition to estimation of deposition characteristics, particle size measurements provide simple measures of quality control for pMDIs and enable a comparison of devices and formulations [22–25]. The most common measure used is the mass median aerodynamic diameter (MMAD), which is a statistical measure of the aerodynamic size of the aerosol and represents the diameter that divides the particle size distribution into two halves with respect to mass (i.e. 50% of the mass lies in particles above and below the MMAD). MMAD is most often measured using inertial impaction particle size techniques such as cascade impaction or via multistage liquid impingement analytical devices. These methods have been adopted as pharmacopoeial standards for various devices, including the pMDI [26,27]. Various systems exist for these types of particle size techniques, which often yield a different quantity and quality of information. Consequently, data must be carefully analyzed for meaningful interpretations to be made [28]. In addition to MMAD, other parameters obtained from these particle sizing techniques that may assist in prediction and assessment of lung deposition include the geometric standard deviation (GSD), fine particle fraction (FPF), and others such as non-balistic fraction (NBF) [29].

Other in vitro methods have been employed to evaluate pMDI performance. These include spray pattern and geometry measurements [30], plume velocity calculation [31], spray temperature determinations [32], and spray force measurements [32].

3.5. Relevance of in vitro and in vivo measures of performance

Analyses of lung deposition of particles from a wide variety of sources have confirmed that the extent of particle deposition within the respiratory tract is related to aerodynamic particle size [33]. However, there is also evidence to suggest that fine particle fractions and MMADs alone do not provide sufficient information to predict the respirability of aerosols [29,34]. With pMDIs, significant deviation of in vitro results from in vivo experiments appears to result from the unrealistic inlet tubes or throats that are used in most cascade impaction and liquid impinger systems [34]. It has been suggested that in vitro and in vivo correlations can be improved by using anatomic throats [35], various breathing patterns [14], and also by incorporation of other factors such as non-ballistic fraction and GSD into the model rather than MMADs alone [29]. Depending on

the goal of the particle size testing these correlations may be relevant. Particle size measurements are important for quality control, comparisons of formulations and devices, and can also be used to indicate relative amounts of lung deposition. They cannot be used, however, to demonstrate clinical efficacy. Ultimately pharmacodynamic and clinical studies will be required to demonstrate equivalence or efficacy and safety of reformulated products with dosage regimen changes.

3.6. Strategies for pMDI optimization and improving performance

Unfortunately, a great deal of device design and formulation development of pMDIs has been performed empirically. A satisfactory clinical response matched with low apparent systemic adverse effects have been interpreted as successful delivery markers for anti-asthma medications delivered via the inhalation route. As a consequence, pMDIs are not optimized systems. Often-cited disadvantages of this type of device are the low efficiency of lung deposition (often only 20% of the emitted dose reaches the lungs) [36] and poor inhaler technique [37]. These outcomes are inter-related and must both be addressed to improve the performance of pMDI device/formulation combinations. What is required is a systematic evaluation of the influence of formulation factors and device parameters on clinical outcomes. However, direct in vivo evaluations of the effect of these formulation and device factors would involve large-scale and costly clinical experiments. The multitude of formulation variables and arrays of different device parameters would mean that even efficiently designed statistical experiments would involve massive matrices of controlled experiments. Thus more investigations are required that bridge different levels of testing such as in vitro measurements and in vivo outcomes, and in vivo assessments and clinical outcomes.

This has been highlighted in recent phenomenological studies relating clinical effect of inhaled corticosteroids to formulation factors [38]. Reformulation of beclomethasone diproprionate as a solution formulation in HFA propellants has resulted in greater peripheral lung deposition of the medication relative to the CFC equivalents that were formulated as suspensions [38]. The greater peripheral lung deposition and reduced oropharyngeal deposition, however, does not correspond to an equivalent increase in therapeutic effect [39]. The HFC formulation resulted in approximately six times more peripheral drug deposition than the CFC product, but only twice the therapeutic effect, raising the issue of required particle size and target region of the lung for optimal inhaled corticosteriod therapy. The particle size that maximizes the therapeutic ratio of a molecule is likely to be different for a beta-adrenergic agonist than for an inhaled corticosteriod. A greater understanding of this relationship will be required if we are to achieve improved drug targeting with future inhalers [40].

Although particle diameter and efficiency of dispersion are the primary variables under the control of the formulator of pMDIs for directing particle deposition in the airways, inspiratory flow rate is also an important factor to consider [41]. Inspiratory flow rate can influence the dose emitted from an inhaler, amount inhaled, oropharyngeal deposition, and regional lung deposition of inhaled medications [41]. Future designs of pMDIs should account for this and integrate systems that emit an aerosol at the correct time and flow rate. Some systems already incorporate breath monitoring and breath-activated aerosols [42,43]. In addition, other patient-related factors such as inhalation techniques, compliance, and misuse need to be addressed. With current pMDI systems, effective use is strongly technique dependent [44,45]. Development of a more 'forgiving' formulation and device may help to reduce the strong dependence of delivery success on patient-related factors [38] (Table 1).

4. Physicochemical characteristics of HFA propellants

Initial screening of alternative propellants identified HFA propellants as likely candidates for replacing CFCs. They appeared to have the necessary physical properties: do not deplete ozone, nonflammable, sufficient vapor pressures, and, importantly, they appeared to be as non-toxic as the CFC counterparts [46]. Although toxicological studies demonstrated the equivalency of HFAs to CFCs [47],

Table 1
In vivo and in vitro endpoints of pMDI performance

Measure type	Endpoint	Methods	Refs.
In vivo	Pharmacokinetic/ pharmacodynamic investigations	Plasma drug concentrations	[17,129,130]
		Physiological markers	
		Toxicity measures	
	Scintigraphic studies	Gamma scintigraphy	[131]
		Single photon emission computed tomography (SPECT)	[132]
		Positron emission tomography (PET)	[133]
	Clinical measurements	Spirometry and peak expiratory flow (PEF)	[134,135]
			[136,137]
		Bronchoprovocation testing	[138]
		Inflammation marker measurement	[139]
		Tissue biopsy	[140]
		Bronchoalveolar lavage	[141]
		Toxicity	[142]
		Quality of life measures	[143]
		Epidemiological studies	
In vitro	Particle size measurement	Inertial methods	[144,145]
		Optical methods	[31,58]
	Spray characterization	Spray force and velocity	[32]
		Plume temperature	[31]
		Spray patterns and geometry	[30]
	Formulation performance	Suspension/solution stability	[59,84]
		Emitted dose	[86]

it was quickly realized that HFA propellants were not 'drop in' replacements for CFCs in pMDIs [48]. While CFCs were good solvents for a number of drug candidates [46], HFA propellants are generally poor solvents for many anti-asthma drugs and excipients currently available for use in pMDIs [5]. These changes in the physicochemical characteristics of the propellant systems impact pMDI design and formulation. A summary of the physicochemical nature of HFA propellants, primarily 1,1,1,2-tetrafluoroethane (HFA 134a), is presented here.

The structures of common propellants are shown in Fig. 2. The physical properties of these propellants and other alternatives have been widely reported in recent years [5,46,48–51]. The physical properties of each propellant (Table 2) can be related to details of the chemical structure and experimental investigations of propellant physicochemical behavior.

HFA 134a and 227ea both have high vapor pressures and low boiling points. These properties

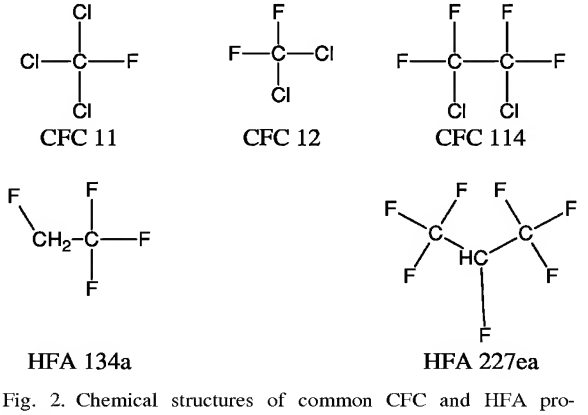

Fig. 2. Chemical structures of common CFC and HFA propellants.

are caused by the strong electronegative repulsive interactions between HFA molecules rather than from non-polar characteristics [5]. In fact, HFAs are relatively polar. HFA 134a contains two electroposi-

Table 2
Physicochemical properties of pMDI propellants

Property	CFC 11	CFC 12	CFC 114	HFA 134a	HFA 227ea
Thermodynamic					
Boiling point (°C)	24	−30	4	−26	−16
Vapor pressure (kPa)	89	566	182	572	390
Enthalpy vap. (kJ/mol)	25.1	17.2	22.1	18.6	19.6
Polarity					
Dielectric constant	2.3	2.1	2.2	9.5	4.1
Dipole moment	0.45	0.51	0.58	2.1	1.2
Induced polarization ($m^3\ mol^{-2} \times 10^5$)	2.8	2.3	3.2	6.1	6.1
Solubility parameter (Hildabrand units)	7.5	6.1	6.4	6.6	6.2
Kauri–Butanol value	60	18	12	9	13
Log *P* (oct/water)	2.0	2.2	2.8	1.1	2.1
Water solubility (ppm)	130	120	110	2200	610
Liquid phase					
Density (g/cm^3)	1.49	1.33	1.47	1.23	1.42
Viscosity (mPa·s)	0.43	0.20	0.30	0.21	0.27
Surface tension (mN/m^2)	18	9	11	8	7

tive protons due to the strongly electron-withdrawing effects of the multiple fluorine atoms attached to the carbon backbone [5]. Similarly, HFA 227ea has one asymmetrical electropositive proton. This polar nature, relative to CFCs, is reflected in the dipole moments and dielectric constants. The polarizabilities of HFAs relative to the CFC propellants are much lower. This illustrates the strong electronegative nature of the fluorine atoms and the strength with which associated electrons are held [5]. An increase in polarizability is associated with increased intermolecular attraction. As a consequence, HFAs are relatively polar but have very low intermolecular attractive forces when compared with CFCs systems.

The most apparent impact of these differences between HFAs and CFCs is insufficient capacity to solubilize traditional surfactants [48,49]. Thus, it is surprising that relatively few published studies have investigated the solubilization capacity of HFAs [49,50,52,53]. Using co-solvents such as ethanol or other solubilizing agents, the solubility of surfactants, drug substances, and excipients in the HFA propellants can be increased [5,53,54]. However, if surfactants are required in a co-solvent-free system (for stability of a suspension formulation), alternative surfactants need to be used [5,55].

Many pMDI formulations contain multi-component mixtures of propellant blends and co-solvents. Therefore, it is important to consider the physicochemical characteristics of these systems in order to understand the effects of formulation variables on product performance. Density, molar volume, and vapor pressure are thermodynamic parameters that assess intermolecular forces within mixtures and are readily measurable in pMDIs [56]. These can be evaluated by comparing theoretical calculations of ideal mixtures with the experimental measurements of real solutions. Propellant systems that have been studied with regard to propellant-driven pMDIs include HFA 134a/ethanol, HFA 227ea/ethanol, and HFA 134a/HFA 227ea mixtures [5,53,56]. These three miscible components may allow the formulator to select appropriate densities (for suspension stability), solubility characteristics (for solution and suspension formulations), and also modify the emitted particle size via non-volatile composition effects [5,53]. Tzou [56] recently demonstrated that the observed densities of HFA 134a/ethanol and HFA 134a/HFA 227ea mixtures closely matched ideal mixture predictions. Vervaet and Byron [5] reported similar result for HFA 134a/ethanol, HFA 227ea/ethanol, and HFA 134a/HFA 227ea mixtures. However, when vapor pressure behavior was investigated,

positive deviations from Raoult's law were observed with HFA 134a/ethanol and HFA 227ea/ethanol mixtures [5,53,56]. Blends of HFA 134a and HFA 227ea did not show any significant deviation from theory [56,57]. Vervaet and Byron explain the apparent atypical observation of deviations from Raoult's law with no accompanied changes in density as a surface phenomenon [5]. HFA propellants have a higher affinity for the gas–liquid interface than ethanol, which, in turn, is surrounded by HFA molecules. In addition, positive deviations from Raoult's law with HFA/ethanol mixtures indicate that the intermolecular forces between the components of the mixture (i.e. between ethanol and HFA molecules) are less than that between molecules of the pure constituents [53,56]. It was suggested that this positive deviation in vapor pressure will allow formulators to use higher concentrations of ethanol (for improved solubility) than would be predicted by ideality without detrimental effects on droplet size or aerosolization [5]. However, recent evidence suggests that increasing ethanol concentrations by 10% w/w will have a significant impact on MMAD and droplet size, as discussed below [53,58].

5. Influence of formulation variables

The influence of formulation variables will now be discussed in the context of these physicochemical characteristics and the above-mentioned measures of performance.

5.1. Solution or suspension formulations?

The active drug substance in pMDIs is either suspended or dissolved in the propellant or propellant mixture (Table 3). Partial solubility of suspended drug is undesirable as it leads to crystal growth via a process known as Ostwald ripening [59]. As a consequence, particle size changes and irregular emitted doses may result. However, if a

Table 3
Common marketed pMDIs and their general composition

Therapeutic group	Drug	Surfactants/ excipients	Propellant system	Formulation type
Bronchodilators				
Maxiair	Pirbuterol acetate	Sorbitan trioleate	CFC 11, CFC 12	Suspension
Maxair Autohalor	Pirbuterol acetate	Sorbitan trioleate	CFC 11, CFC 12	Suspension
Proventil	Albuterol sulfate	Oleic acid	CFC 11, CFC 12	Suspension
Proventil HFA	Albuterol sulfate	Oleic acid	HFA 134a, ethanol	Suspension
Tornalate	Bitolterol mesylate	Ascorbic acid, saccharin, menthol	38% w/w ethanol, CFC 11, CFC 12	Solution
Ventolin	Albuterol sulfate	Oleic acid	CFC 11, CFC 12	Suspension
Ventolin HFA	Albuterol sulfate	None	HFA 134a	Suspension
Corticosteriods				
Aerobid	Flunisolide	Sorbitan trioleate, menthol	CFC11, CFC 12, CFC 114	Suspension
Azmacort	Triamcinolone acetonide		CFC 12, 1% w/w ethanol	Suspension
Beclovent	Beclomethasone dipropionate	Oleic acid	CFC 11, CFC 12	Suspension
Becotide 100	Beclomethasone dipropionate	Oleic acid	CFC 11, CFC 12	Suspension
Flovent 44, 110, 220	Fluticasone propionate		CFC 11, CFC 12	Suspension
QVAR 50, 100	Beclomethasone dipropionate		HFA 134a, ethanol	Solution
QVAR Autohaler 50, 100	Beclomethasone dipropionate		HFA 134a, ethanol	Solution
Vanceril	Beclomethasone dipropionate–trichlorofluoromethane clathrate		CFC 11, CFC 12	Suspension
Other anti-inflammatory				
Intal	Cromolyn sodium	Sorbitan trioleate	CFC 11, CFC 12	Suspension
Tilade	Nedocromil sodium	Sorbitan trioleate	CFC 11, CFC 12	Suspension

solution formulation is chosen the drug must have sufficient solubility to allow therapeutic doses to be delivered with a few actuations (usually two) of the device. Thus, careful selection of drug form and propellant system from solubility studies and compatibility investigations is required in pMDI development. In suspension systems, the predominant factor limiting the minimum emitted droplet size is the size of the suspended particles that will be contained within aerosol droplets [60–62]. In solution systems, however, the droplet size is primarily governed by factors such as the non-volatile fraction, vapor pressure, actuator design, and the physicochemical nature of the liquid formulation [62]. With a limited range of propellant systems available, the selection of a solution or a suspension system may be by necessity rather than by choice. However, it should be recognized that each system has distinct formulation requirements and may have certain advantages for a given drug substance. Suspensions require very low solubility of the drug in the formulation. This usually results in good chemical stability of the drug [63]. However, aggregation and rapid flocculation of suspension systems may require addition of stabilizing excipients such as surfactants. In solution systems, high solubility and good stability of drug in the propellant system is required. Most current formulations are suspension systems containing micronized drug with particle sizes between 2 and 5 μm [64].

5.2. Effect of vapor pressure

5.2.1. CFC studies

One of the first investigations of the influence of formulation factors on particle size was performed by Polli and co-workers [65]. Using suspension systems in CFC propellant blends, the effect of a number of formulation factors, including vapor pressure, was studied. Increased vapor pressure resulted in decreased aerosol particle size, ultimately to the size of the suspended particle when the vapor pressure of the formulation was 77 psig. When temperature was used to modify vapor pressure, similar trends were also seen. Subsequently, a number of studies have been performed that demonstrate that the vapor pressure in CFC systems has an inverse relationship with emitted particle size [66,67]. Moren demonstrated that increased vapor pressure resulted in an increase in deposition on the device, but reduced deposition in the mouths of subjects [68]. Scintigraphic studies have also shown that vapor pressure has an effect on lung deposition patterns. Newman et al. performed a scintigraphic lung deposition study with suspension systems and showed that an increase in the vapor pressure resulted in a decrease in extrathoracic deposition and an increase in whole lung deposition [69]. Similarly, Harnor and co-workers showed that a high vapor pressure aerosol (488 kPa) resulted in decreased amounts of swallowed formulation relative to a low vapor pressure formulation (255 kPa) [67]. However, the change in vapor pressure in this study did not result in an increase in the proportion of peripheral lung deposition (measured using penetration index).

5.2.2. HFA systems

HFA propellants have higher vapor pressures than their CFC counterparts. As previously mentioned, the vapor pressures of HFA systems have been investigated and are shown to have positive deviations from Raoult's law when ethanol is used. The effect of vapor pressure as a droplet size modifier in HFA systems has only recently been studied systematically [53,58]. In these investigations, increasing fractions of ethanol in HFA 134a propellant pMDIs resulted in changes to solvency and particle size in solution systems. Despite positive deviations of vapor pressure, effectively decreasing the differences in vapor pressure between formulations with 2.5, 10, 20, and 50% w/w ethanol, significant particle size differences were still detected between all formulations using cascade impaction analysis. Work has yet to be performed to determine the clinical significance of these particle size changes (Table 4).

In a recent study by Williams et al. using blends of HFA 134a and 227ea, increases in the concentration (mole fraction) of HFA 227ea resulted in increases in droplet size (Fig. 3) [70]. The authors relate this droplet size to the decrease in vapor pressure that results from increased concentrations of HFA 277ea in the system. However, this may be only part of the explanation, as the correlation of droplet size increases to the changes in vapor pressure was distinctly non-linear (Fig. 4). At low concentrations (mole fraction) of 227ea (at 24 °C) there is a steep decrease in vapor pressure as 227ea fractions increase. At

Table 4
The effect of increasing proportions of ethanol on HFA 134a solution pMDI aerosol characteristics [58]

HFA composition:	97.5% HFA		90% w/w HFA		80% w/w HFA		50% w/w HFA	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
MMAD (μm)	0.48	0.02	0.55	0.04	0.69	0.09	1.54	0.31
GSD	2.26	0.13	2.61	0.22	3.19	0.23	4.98	0.88
Fine particle fraction (FPF)	0.51	0.14	0.34	0.02	0.18	0.02	0.05	0
Emitted dose (μg)	17.25	1.23	16.16	0.76	14.42	0.76	13.09	0.78
Device (μg)	0.23	0.05	0.12	0.01	0.12	0.02	0.3	0.01
USP Throat (μg)	0.25	0.09	0.5	0.03	0.67	0.04	0.63	0.01

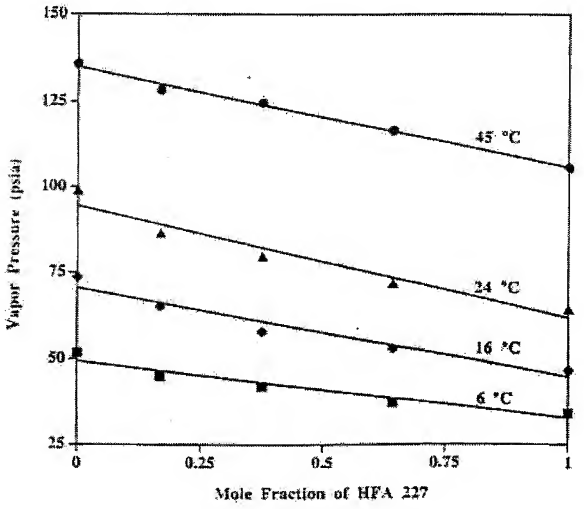

Fig. 3. The influence of propellant composition on the total vapor pressure of HFA 134a and HFA 227ea propellant blends (from Ref. [70]).

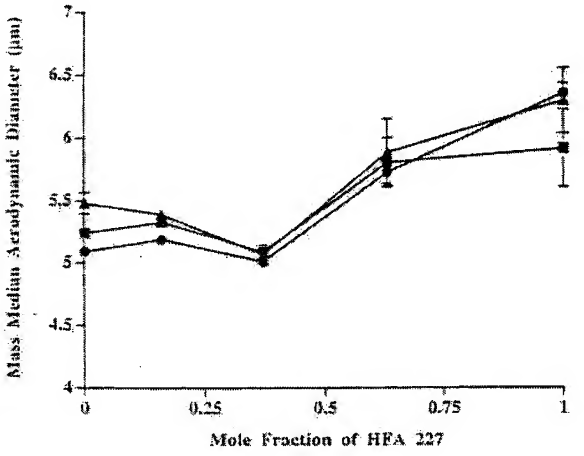

Fig. 4. MMAD of a triamcinolone acetonide-based pMDI formulation containing HFA 134a and HFA 227ea at different compositions determined at beginning (squares) and end (circles) actuations of the canister, and after 3 months storage at 24 °C/60% RH (triangles) (from Ref. [70]).

higher 227ea concentrations, the curved relationship between vapor pressure and 227ea concentration (mole fraction) plateaus. Alternatively, inspection of the MMAD versus concentration of 227ea shows no increase in MMAD at low 227ea levels (less than 0.46). Increases in MMAD were greater when concentrations of 227ea were above 0.5. Steckel and Muller also investigated the effect of ethanol on the fine particle fraction emitted from HFA 134a pMDIs using a two-stage liquid impinger [71]. Decreasing levels of ethanol, from 10, 5, and 2% w/w, resulted in an increase in FPF. Brambilla et al. compared the MMAD resulting from pMDIs containing either HFA 134a (higher vapor pressure: 550 kPa) or HFA 227ea (lower vapor pressure: 350 kPa) in otherwise identical formulations [72]. A MMAD of 3.5 μm resulted from the HFA 227ea pMDI, while a MMAD of 2.8 μm resulted from the HFA 134a system. The authors demonstrate that an increase in vapor pressure leads to finer aerosols, but also demonstrate that there is little change in the fine particle fraction. It was suggested that, in combination with predictable changes due to orifice modifications, the MMAD and FPF could be modified independently of each other using vapor pressure. These findings differ from those described in HFA 134a/ethanol systems where ethanol was used as a vapor pressure modifier [58]. The difference arises from the fact that vapor pressure alterations caused by ethanol also change the non-volatile fraction of the formulation, whereas

use of the lower vapor pressure HFA 227ea does not contribute to non-volatile concentrations. The influence of other non-volatile excipients used in pMDIs is discussed below. With further study, it would seem possible that the combination of propellants, co-solvents, and device characteristics may be chosen judiciously such that MMAD and FPFs could be calculated or even predicted accurately from a knowledge of key physicochemical properties.

Several phenomenological studies comparing HFA systems with CFC pMDIs have shown that HFA systems produce smaller droplets [38,73]. Leach [38] demonstrated that an HFA 134a solution formulation of beclomethasone dipropionate produced an aerosol cloud that was warmer, 'softer', and longer, with a smaller particle size, than the CFC alternative formulation. The HFA system was also shown to result in greater lung and reduced throat deposition. Many of these characteristics can be related to the changes in the physicochemical nature of the propellant system such as vapor pressure. However, without a full understanding of each factor, optimal pMDI design will be difficult.

5.2.3. Vapor pressure effects in terms of mechanisms of atomization

Vapor pressure is the primary physicochemical property that determines the speed and rate of evaporation. The pMDI formulation, inside the aerosol canister, is kept under constant pressure according to the vapor pressure of the formulation. When the valve is opened, the formulation is released under this pressure gradient at high speeds [73]. Thus, a formulation with a high vapor pressure will exit the atomization nozzle at high speeds and will have rapid evaporation. The high speed ejection from the orifice is linked with shear-thinning, a process whereby liquid sheets or large droplets are broken into smaller droplets as they interact with stagnant air [74]. Production of an aerosol is a rather complicated process to describe mathematically due to multiple factors involved with the transient, cavitating turbulent fluid that rapidly flashes into evaporating droplets [19]. However, an empirical relationship that allows reasonable agreement between functions of vapor pressure and the emitted mass median diameter (MMD) (Eq. (1)) has been described [75] (cited in Ref. [76]):

$$D_{0.5} = \frac{8.02}{q_{ec}^{0.56}[(p_{ec} - p_{\infty})/p_{\infty}]^{0.46}} \quad (1)$$

where $D_{0.5}$ is the MMD, q is a flow quality parameter from the Rosin–Rammler distribution, p_{ec} is the pressure in the expansion chamber while p_{∞} is the ambient pressure. This relationship demonstrates the importance of vapor pressure and flow quality in determining particle size in pMDIs. This correlation, developed using CFC-based systems, has also shown good consistency with experimental observations in HFA 134a systems [76]. It must be noted, however, that these predictions were only useful for determination of droplet size at the orifice exit, not downstream in the aerosol plume. With these factors taken into account, vapor pressure is clearly an important consideration for the development and demonstration of particle size equivalence in pMDI systems and for the optimization of the performance of pMDI systems. In many of these studies, however, the influence of confounding variables introduced by modulation of vapor pressure has not been explored. The addition of ethanol to HFA 134a will result in changes to the formulation that may influence atomization characteristics, including viscosity, heat capacity, and preponderance of nucleation sites for bubble growth. Such factors need to be investigated. Also, the clinical significance and targeting potential of pMDIs modified using vapor pressure needs systematic evaluation.

5.3. Drug concentration and drug substance

In addition to investigating the effect of vapor pressure, Polli et al. also investigated the effect of drug concentration on the aerosol particle size emitted from suspension pMDIs [65]. At high drug concentrations (2.86 mg/g) MMAD increased significantly (18 μm versus 3.2 μm) over the MMAD of lower drug concentration formulations (0.175, 1.43 mg/g). The increase in particle size was possibly related to decreased propellant fraction and decreased efficiencies of atomization at the nozzle (due to agglomerate interactions) and at the expansion chamber. Atkins also showed that the respirable

fraction of a model compound was decreased with the addition of higher drug concentrations [77]. Similar conclusions have been reported by other authors [72,78]. Drug concentration is also related to the stability of suspension systems and may affect the uniformity of the emitted dose [31]. Factors affecting suspension stability are discussed below. Valve clogging may occur at higher drug concentrations and an apparent limit has been suggested to be 2% w/w or 20 mg/ml [78].

The effect of drug properties affecting aerosol behavior was recently reviewed by Suarez and Hickey [79]. Drug properties such as particle size, lipophilicity, molecular weight, and crystal form influence dissolution rate and absorption. The performance of anti-asthma medications may be improved by modifying these characteristics. Selection of the drug form was shown to be an important factor in chemical and physical stability of albuterol-containing pMDIs in CFC and HFA systems [80]. These observations were related to drug solubility and aggregation characteristics in propellant systems. Drug form selection, minimization of amorphous content, and stability of drug polymorphs are important considerations in minimizing drug solubility and crystal growth in suspension systems [5]. The use of combinations of drug substances within a single pMDI has also resulted in formulation challenges due to hetero-aggregate formation in suspension systems [64].

Drug particle manufacture is also an important factor to consider [5]. Micronization and milling techniques frequently cause changes to the crystalline structure of the drug substance [81]. Alternative particle manufacture methods are discussed in detail in other reviews in this issue (York and co-workers, Chan and co-workers).

5.4. Surfactants

Surfactants traditionally used in CFC-based pMDIs are not soluble in HFAs without the use of co-solvents [5]. However, the use of co-solvents, such as ethanol, is most likely incompatible with suspension formulations as drug solubility will also be promoted. Thus alternatives to using these surfactants are being sought. Several alternative surfactants have been suggested but their use remains limited by an insufficient toxicological profile with respect to lung delivery.

Surfactants were incorporated into CFC pMDIs for several reasons. In suspensions, surfactants have been used to stabilize the dispersion by reduction of the electrostatic charge of the micronized drug [59,63]. Surfactants may help solubilize drug and prevent crystal growth during storage in solution formulations [63]. In addition, typical pMDI devices need surfactants for valve lubrication over 100 to 400 doses [5,63]. Recently, some have suggested that non-volatile excipients in HFA systems, such as surfactants, may be useful in modifying particle size where the objective is to produce aerosols that are therapeutically equivalent to CFC predecessors [72]. Currently approved surfactants for use in pMDIs include oleic acid, sorbitan trioleate, and soya-derived lecithin [82]. The solubility of these in HFA 134a ranges from 0.005 to 0.02% w/v, much lower than the concentration required to stabilize CFC suspensions (0.1–2.0% w/v) [49].

The effect of surfactants on emitted droplet size has been investigated by several groups. In the early work performed by Polli et al. the surfactant sorbitan trioleate decreased the MMAD of the CFC dexamethasone suspension when added to the formulation [65]. A suspension of terbutaline in a CFC system containing sorbitan trioleate surfactant was shown to have little change in emitted particle size when either 2.8 or 14 mg/ml of surfactant was added [66]. Interestingly, the surfactant had a significant effect on the obscuration (droplet concentration) of the laser diffraction instrument used to determine particle size. Surfactants may lead to an increase in MMAD due to decreased evaporation rates from aerosol droplets. This may occur because of their tendency to associate at the air–liquid interface [62].

5.4.1. Suspension stability

Suspension stability in pMDIs is critical to their performance. If suspensions are unstable, the dose emitted and particle size characteristics may be unpredictable and will lead to poor therapy. The theory of aerosol suspension stability has been reviewed by Johnson [59]. Stability can be assessed by measuring sedimentation rates and heights [83], particle size changes via laser light scattering and reflectance methods [64,84], microscopy [85], and

dosage uniformity experiments [86]. Instability may occur via creaming (phase separation) or coalescence (aggregation) [78]. Flocculation may precede coalescence, whereby suspended particles aggregate together under weak van der Waals forces that are broken upon shaking. Stokes' law describes the sedimentation velocity of a suspended particle, and can help predict important factors that determine the rate of creaming:

$$v = \frac{2gr^2(d_2 - d_1)}{9\eta} \quad (2)$$

where v is the sedimentation rate of a spherical particle, g is acceleration due to gravity, r is the particle radius, d_1 and d_2 are the densities of the continuous phase and dispersed phase, respectively, and η is the viscosity of the continuous phase. Thus, the densities of the propellant system should be blended, where possible, to match the density of the drug particles [87]. Particle size reduction is also an option to reduce sedimentation rates.

Interparticulate interactions can similarly be discussed using the theory of suspension stability developed by Derjaguin and Landau [88], and Verwey and Overbeek [89] (DLVO theory). DLVO theory is not well developed for non-aqueous systems such as seen with the pMDI propellant environment and therefore its use is somewhat controversial [5,90]. Electrostatic effects have some influence on suspension stability, but it is reported that steric forces may be more significant [5,90]. Manipulation of steric forces between drug particles using surfactants has been critical in achieving stable CFC suspensions. Use of alternative surfactants in HFA systems may allow similar stability concerns to be addressed. Byron et al. [91] showed that pre-coating of particles with traditional surfactants for HFA suspensions had some stabilizing effect. Blondino and Byron [50] performed a large number of solubility determinations for alternative surfactants in alternative propellants. Recent overviews of the patents issued in this area have been reviewed [8,54,92,93]. Wright described promotion of suspension stability in HFA 227ea using a variety of polymer- and surfactant-based excipients [55]. Stefely et al. [54] describe the use of oligolactic acid-based excipients (amphiphiles) in HFA systems. Superior dose uniformity performance was demonstrated in suspension HFA systems over systems without the amphiphilic excipient added. Recently, surfactant complexation methods have been described as an approach to increase solubility and also aid suspension stability [94]. Williams used a co-grinding technique to improve the performance characteristics of a triamcinolone acetonide suspension in blends of HFA 134a and 227ea [95]. The surfactant Pluronic F77® was co-grinded with the drug, and suspended in the propellant system. The MMAD was decreased and FPF increased at the same time as the physical stability of the suspension was promoted.

Surfactant stabilization is not always suitable or predictable. Many of the interactions of surfactants with drug particles for suspension stabilization are drug specific. Furthermore, surfactants with lowered solubility in HFA systems can be irreversibly precipitated out of solution by competing dipolar molecules such as water [50]. Also, surfactant-stabilized suspensions may have sub-optimal aerosolization properties [96]. Accordingly, some research efforts have been directed toward particle engineering as a method to improve suspension stability. Weers et al. and Dellamary et al. describe the use of hollow porous particles to decrease the attractive forces between particles in suspension [90,97]. The similarities between the particles and the dispersing medium (the propellant system enters and fills the porous particles) reduces the effective Hamaker constant, which corresponds to forces of attraction, and also makes the density difference between the propellant and particles smaller. The FPF of these aerosols was reported to be around 70%.

5.4.2. Solution stability

Due to increased solubility of certain drugs in HFA propellants, CFC suspension systems have been reformulated as solution systems in HFA propellants [82,98]. The extent of drug solubility in propellant systems can be assessed using methods described by Dalby [99]. Non-ionic forms of drug substance are usually preferred in solution systems [5]. The formulators major concerns with solution systems are the possible reduction in chemical stability [100], achieving adequate drug concentration for a conveni-

ent dosing regimen, and drug loss by partitioning to container and valve components [5]. Surfactants may be used to improve solubility and also to alter the chemical stability of the drug in solution systems [101]. Additionally, physical stability may also be an issue if the limit of solubility in a system is close to the solubility required for dosing regimens. Ingress of water, which shows a high affinity for HFA propellants [5], may result in precipitation of the drug.

Recent attempts have been made to correlate solubility parameters and partition coefficients to the solubility of substances in HFA propellant systems [52,53]. There was no apparent relation between solubility in HFA and the Fedors solubility parameter, or with the solubility parameter calculated from the method of van Krevelen. When log solubility versus CLOGP was plotted, there was a linear relation for some of the compounds exhibiting a finite solubility in the HFA propellants [52]. Thus the prediction of drug solubility may be limited using common methods.

5.5. Inverse micelles and disperse systems

Reverse micelles and microemulsions have been used to promote solubility of substances in hydrocarbons and CFCs [102–105]. Evans et al. dissolved hydrophilic compounds in CFC systems using lecithin to form inverse micelles (Fig. 5) [102]. Warren and Farr used soya phosphatidylcholine in CFC propellant blends to achieve solubilization of salbutamol and triamcinolone acetonide [106]. Sommerville showed that a number of compounds could be solubilized in alternative propellant systems (dimethyl ether and propane) using inverse micelle systems. The performance of these pMDI systems was determine by particle size analysis and was shown to have fine particle fractions greater than commercialized pMDIs [107]. Since there may be multiple critical micelle concentrations in non-aqueous solutions, definition of the drug solubilizing concentration is important [74]. Few studies have investigated these systems in HFA propellants [108,109].

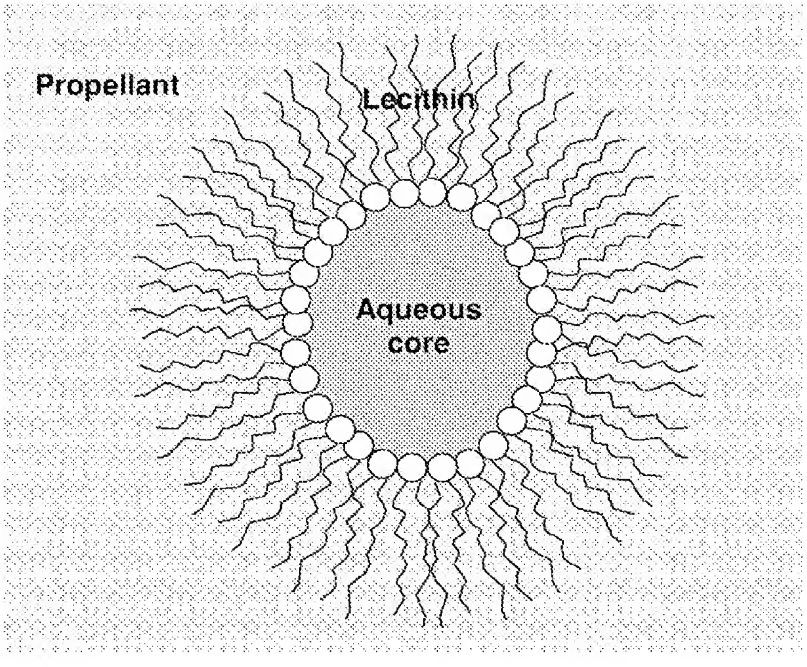

Fig. 5. Schematic diagram of a lecithin-based reverse microemulsion system.

5.6. Electrostatics

Aerosolization can induce static charges by tribolelectrification [110]. Charged aerosols may lead to different patterns of deposition in device components and in the lungs. In spacer devices used with pMDIs, an inverse relationship between respirable fraction and static voltage was shown [111]. Prewashing the spacers in soapy water may eliminate static in the local environment and result in higher respirable fractions. In a study by Peart et al. the electrostatic charges present on the fine particle dose of several CFC and HFA albuterol pMDIs was evaluated [110]. Ventolin (CFC) and Airomir (HFA) had similarly charged aerosols despite different propellant systems, drug salt, drug concentration, and metered volumes. It appeared the drug substance and propellants had significant effects on the electrostatic properties of the fine aerosol cloud. Thus, if electrostatic deposition is deemed significant, selection of device components and formulation additives may result in decreased losses of the fine aerosol particles to charged surfaces other than the target site.

5.7. Other propellants

In the search for alternative propellants for pMDIs, several important desirable characteristics were detailed: the propellants should be safe for humans and the environment, inexpensive, and have suitable characteristics for aerosol production. Amongst those propellants meeting these requirements was dimethyl ether (DME), and low-molecular-weight hydrocarbons such as propane and butane. Hydrocarbons are available in a wide range of solvencies, vapor pressures, and boiling points. DME, a known solvent, has been shown to dissolve a wide range of surfactants of varying polarities [50]. However, hydrocarbons have very low densities, and are potentially flammable and more reactive than CFCs [46]. Flammability of these propellants may be important during manufacture, but in terms of pMDI safety, flame extension from these devices is very small so it is unlikely to be a real concern [63]. Despite these potential disadvantages, and the industry focus on HFA propellants, DME and hydrocarbons remain possible future candidates for propellants.

Compressed gases, such as carbon dioxide, nitrous oxide, and nitrogen, have received little attention as possible propellant alternatives. This is primarily due to the gradual pressure drop inside the canister as the product is depleted. Without the advent of specifically designed valves to account for this change in internal pressure, compressed gases will unlikely be used in pulmonary pMDIs, but use in nasal delivery devices has been suggested [63]. Liquefied gases, such as carbon dioxide and nitrous oxide, may play a role in future pMDIs. However, due to the much greater pressures, these pMDIs would require new processing methods and changes to the canister and valve technology [63].

5.8. Microbiological growth

The potential of propellants to support microbial growth has not been widely reported but it is a critical performance criterion for pMDIs. Meier et al. reported comparable microbiological growth profiles for HFA 134a and CFC propellants [112] (cited in Ref. [82]). The effects of propellant blends and excipients on microbial growth potential need to be investigated.

6. Influence of device variables

In pMDIs, the container and valve are integral components to the performance of device and formulations. With the transition from CFCs to alternative propellants it has become recognized that these device components cannot be considered independently of aspects of the pMDI formulations. Early on it was observed that valves developed for use with CFCs had different performance when used with HFA propellants [113]. Thus a review of how device variables influence pMDI performance with alternative propellants is necessary.

6.1. Valve and container design

The early success of pMDIs can be related to the development of a metering valve that allowed reproducible amounts of drug to be repeatedly delivered from an aerosol canister. Most pMDIs are fitted with a valve to be used in the inverted position

rather than using dip tubes. Typical metered volumes range between 25 and 100 μl. During manufacture, the valve is often crimped to the neck of the container and then filled, under pressure, through the valve stem. Traditional valves used in pMDIs have a metering chamber that is filled following an actuation (depression of the valve stem). Until the phase-out of CFCs, little changes had occurred in valve technology due to the wide applicability of designs to the relatively narrow range of propellant blends used in pMDI formulations [113]. However, with HFA formulations, valve material changes were required to achieve adequate compatibility and device performance [8,114]. For example, nitrile elastomers were observed to have 10 times the leak rate with HFA 134a propellants compared to HFA 227ea propellants [113]. In addition to leak rates, the major issues relating to valves have been extractables, drug adsorption, 'loss of dose' and 'loss of prime'effects, and dose variability changes. Many of these issues have been highlighted in a draft guidance document from the U.S. Food and Drug Administration (FDA) on the chemistry, manufacturing, and controls (CMC) for pMDIs and dry powder inhalers [115]. Methods and rationale of extractables and leachables detection in pMDIs have recently been presented [116]. A number of potential extractables have been identified for different polymer types that are present in valve components and include nitrosamines, polynuclear aromatics, mercaptobenzthiazole, among others. Some specific extractables have known toxicity under certain exposure conditions and therefore require appropriate monitoring procedures. Loss of prime occurs when the contents of the metering chamber vary (decreases) during storage. Newer valve designs have been investigated to improve these characteristics [91,113,117]. Details on newer valve designs are also found in the patent literature [93].

Containers have been subject to similar scrutiny and changes. Typically, containers are internally coated aluminium canisters. Coatings prevent interactions between the canister and the formulation such as drug loss by adsorption, corrosion of the aluminium, and catalysis of chemical degradation of the drug. Common coatings include epoxy resins, anodized aluminum, epoxy-phenol, or perfluoroalkoxyalkane coatings [93,118,119].

Thus, component selection is an integral part of the development of pMDIs. Components should be evaluated for compatibility (chemical and physical), mechanical strength, consistency, and potential extractables. These tests should be performed under stress conditions to identify potential failure modes [30].

6.2. Actuator design

Actuators are important for the production of appropriate aerosols. These can influence the particle size of the droplets and also the nature of the aerosol plume emitted from a pMDI [9,74,120]. Therefore, appropriate selection of the actuator is critical for optimal pMDI performance.

Reducing the spray orifice diameter has been shown to reduce the particle size and alter the FPF of pMDIs [65,106,120–122]. In the investigation of Polli et al., orifice diameter was decreased from 0.076 to 0.061 cm without a decrease in MMAD of the suspension CFC formulation [65]. However, a further reduction from 0.061 to 0.046 cm resulted in a decrease from 11 to 3.2 μm MMAD. Warren and Farr showed a strong dependency of the fine particle dose with orifice size in CFC micellar solution formulations [106]. As a consequence of the smaller orifice, a wider spray cone was produced that results in significantly greater deposition on the actuator rather than the throat of the cascade impactor. Thus the non-respirable fraction had clinically preferable deposition patterns over larger orifice diameter actuators.

In a HFA solution formulation, MMAD was not affected by a reduction in orifice diameter (0.42 to 0.25 mm), but the fine particle dose was significantly increased [120]. Similarly, Brambilla et al. showed that a solution HFA formulation had marked increases in fine particle dose and small decreases in MMAD with a reduction in the orifice diameter. Dunbar and Hickey used a mathematical model of fluid flow and atomization processes during an actuation of a pMDI to show that the median droplet diameter was influenced by an interaction between the actuator orifice and metering chamber valve orifice [123]. An inertial impaction was also influenced by a similar interaction. Optimization of actuator design may be achieved using similar

methodologies. In addition to traditional actuator designs, many novel and modified designs have been reported [63]. Amongst these are breath-triggered actuators used to improve the coordination of inspiratory effort with aerosol plume production [63]. An example of this type of actuator is the commercialized Autohaler™ device. This device is flow actuated, so that when the patient's inspiratory flow exceeds 30 l/min, actuation occurs. Mechanical break-up actuators have also been investigated to increase the efficiency of atomization when some formulations with a high non-volatile fraction are used [63,124].

Holding chambers and spacers have also been extensively investigated in combination with pMDIs. These add-on devices have frequently been used due to poor inhaler technique and poor coordination of actuation and inspiration with pMDIs [125]. Related issues in pMDIs is the high throat deposition and 'cold freon' effect [32]. Thus spacer devices, by extending the distance between the orifice and the mouth of the patient using a chamber: reduce oropharyngeal deposition of the aerosol, eliminate the 'cold freon' effect, reduce the poor deposition patterns that result from coordination difficulties, and also allow evaporation from emitted droplets. The performance of spacers varies considerably from brand to brand and is also related to the pMDI device used [126–128].

7. Conclusions

There are a multitude of formulation factors to consider when developing a pMDI. Evaluation of each of these variables has been performed over the years but there has been an abundance of different approaches in the determination of the effects on device performance. Thus, although much is known about pMDI on the empirical level, a systematic approach has been clearly missing. With the introduction of alternative propellant systems, the opportunity to establish relationships between different levels of testing such as in vitro measurements and in vivo outcomes, and in vivo assessments and clinical outcomes, has arrived.

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